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Abstract

Gabapentin (Neurontin®) is an antiepileptic drug commonly prescribed for pain treatment. In the past 15 years, indications for gabapentin have been increasing even though the complete mechanism of action is unknown. Side effects include somnolence, dizziness, ataxia, nystagmus, and fatigue. This study reviewed all cases positive for gabapentin submitted to the Washington State Toxicology Laboratory between January 2003 and December 2007. The concentrations of gabapentin in blood from impaired driving cases (n = 137) ranged from < 2.0 to 24.7 mg/L with a mean of 8.4 ± 5.4 mg/L and a median of 7.0 mg/L. The driving population was 50% male with a mean age of 43.0 ± 10.9 years (range 23–73). Of the cases studied, only 7% were positive for gabapentin alone with the remaining 93% indicative of polydrug use. Drug Recognition Expert reports from four cases in which the only drug detected likely to be causing impairment was gabapentin were examined. These reports demonstrated that subjects may exhibit psychophysical indicators of a central nervous system depressant (e.g., horizontal gaze nystagmus, poor performance on standardized field sobriety tests) with clinical indicators (e.g., dilated pupils, low body temperature, and elevated pulse and blood pressure) that are not consistent with a depressant.

Introduction

Gabapentin (Neurontin) is a drug prescribed for the treatment of partial seizures or neuropathic pain. It was first approved in the United States by the Food and Drug Administration in 1993 as an adjunct therapy for treatment of partial seizures. In 2004, gabapentin was approved to be used as a treatment for neuralgia. Currently, gabapentin is also being prescribed for the treatment of bipolar disorder (1), drug/alcohol addiction (2), congenital nystagmus (3), migraines (4), and hot flashes (5). Over 90% of the sales for gabapentin are for off-label prescriptions, keeping it in the top 100 of drugs prescribed in the U.S. (6,7).

The complete mechanism of action for gabapentin is unknown. Although the drug is structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA), gabapentin does not modify the GABA ligand binding, affect the re-uptake or release of GABA, or metabolically convert into a GABA ligand (8). However, there is evidence that gabapentin binds voltage-gated calcium channels (9), which may result in a decrease of neuronal excitability and synaptic transmission (10). In addition, gabapentin may stimulate the noradrenergic system (11).

The recommended dose for gabapentin is 900–1800 mg/day. Previous studies have demonstrated that a 400 mg dose resulted in a maximum blood concentration of 3.4 mg/L (range 2.2–6.1) at 4 h. Patients undergoing chronic therapy for three months averaged trough serum concentrations of 1.9 mg/L for a 900 mg/day dose and 2.6 mg/L for a 1200 mg/day dose (12). Absorption of gabapentin is dependent upon the L-amino acid transporter. There does appear to be a linear relationship between dose and blood concentration at therapeutic dose ranges resulting in 60% oral bioavailability; higher doses will result in decreased bioavailability (13,14). Peak concentrations are reached within 2–3 h of dosing, and the elimination half-life is 5–7 h following a single dose (15). Gabapentin is primarily eliminated as unchanged drug by renal excretion (14).

Similar to other antiepileptic drugs, adverse reactions for gabapentin include somnolence, dizziness, ataxia, fatigue, and nystagmus (16,17). However, there are no published studies concerning the effects of gabapentin on driving. The goal of this study was to examine gabapentin-positive driving cases at the Washington State Toxicology Laboratory (WSTL) for the previous five years.

Experimental

Blood specimens that had been collected in 10-mL grey-stopper tubes each containing 25 mg sodium fluoride and 20 mg potassium oxalate as preservatives (Tyco Healthcare Group LP, Mansfield, MA) were submitted to WSTL by police agencies. All samples were tested for alcohol by headspace gas chro-
matography (GC). Samples with an alcohol result < 0.10 g/100 mL underwent a drug screen performed by enzyme multiplied immunoassay (EMIT, Syva/Dade Behring, Deerfield, IL) for amphetamines, barbiturates, benzodiazepines, benzoylecgonine, opiates, phencyclidine, propoxyphene, marijuana metabolite, methadone, and tricyclic antidepressants. In addition, all samples obtained from vehicular homicide/assault cases had a drug screen performed even if the alcohol result was ≥ 0.10 g/100 mL.

Based on preliminary drug screen results, confirmation assays were performed. The initial confirmatory assay was a liquid–liquid extraction using n-butyl chloride followed by back extraction into hydrochloric acid and then re-extraction into chloroform to detect basic drugs using GC–mass spectrometry (MS). Although gabapentin is not identified using this procedure, a gabapentin breakdown product (-H₂O) is sometimes observed (Figure 1). A specialized assay for gabapentin was performed if the breakdown product was detected or if the submitting agency listed gabapentin as a suspected drug or known medication.

Determination of gabapentin

Stock solutions for calibration containing 100 mg/L gabapentin were prepared in methanol. Working solutions of calibrators were prepared by adding 10, 25, and 50 µL of stock solution to 0.25 mL of blank blood for final concentrations of 4, 10, and 20 mg/L, respectively. Stock solutions for quality control containing 15 mg/L gabapentin were prepared independently.

For each sample, 0.25 mL of blood was spiked with 25 µL of the internal standard [1-(aminomethyl)cycloheptaneacetic acid, 250 mg/L]. Proteins were precipitated by the addition of 2 mL of acetonitrile to each sample. Samples were vortex mixed for 30 s, allowed to stand for 5 min, and then centrifuged at 2000 rpm for 5 min. A 0.1-mL aliquot of the supernatant was removed for analysis.

The extracts were analyzed using selective ion monitoring GC–electron impact-MS (m/z 153, 152, 111). Validation studies were performed for this assay by analyzing concentrations of gabapentin ranging from 1 to 200 mg/L. The assay was linear for gabapentin from 2 to 200 mg/L with a least-squares linear regression analysis correlation coefficient (r²) of 0.999 or better. The limits of quantitation and detection (LOD) were 2 and 1 mg/L, respectively. Accuracy and precision studies were performed with a control spiked at 15 mg/L. The assay was 99.8% accurate (n = 10 within-run) with a coefficient of variation of 4% (n = 10 within-run) and 11% (n = 7 between-run).

In 2007, samples suspected of gabapentin were sent to NMS Labs (Willow Grove, PA) for detection and quantitation by liquid chromatography–tandem MS (reporting limit = 0.10 mg/L).

Results

Blood samples for 23,479 driving impairment cases were submitted to the WSTL by police agencies in 2003–2007. Of these cases, 137 (0.6%) were found to be positive for gabapentin. There was no difference observed between cases in regard to sex (male = 50%), and the average age was 43.0 ± 10.9 years (Table I). The relative frequency distribution of gabapentin concentrations is seen in Figure 2. The mean, median, and range were 8.4 ± 5.4, 7.0, and < 2.0 to 24.7 mg/L, respectively.

There were nine cases in which gabapentin was the only drug detected that was likely to be causing impairment. Of the polydrug cases, benzodiazepines were the most common class of drugs to be detected in addition to gabapentin with 44% of cases being positive; diazepam (12%), nordiazepam (14%), and lorazepam (12%) were the most common. Opioids were detected in 43% of the cases with methadone (15%) and hydrocodone (15%) the most common. Antidepressants were also found in 43% of the cases with citalopram (15%) being the most common. Other CNS depressants were detected in 36% of the cases with diphenhydramine (7%), zolpidem (7%), trazodone (7%), and meprobamate (7%) the most common. Antiepileptic drugs were found in 25% of the cases with lamotrigene (8%) and topiramate (7%) being the most common. The least common class of drugs detected were cannabinoids (15%), stimulants (11%), and ethanol (6%).

Case Histories

Of the 137 driving cases, 74 had a Drug Recognition Expert (DRE) evaluation performed. There were only four cases where gabapentin was the only drug detected likely to be causing impairment, and a complete DRE evaluation was performed. Table II gives a summary of the standardized field sobriety tests (SFSTs), and Table III summarizes vital signs observed in the evaluations for gabapentin-only driving cases.

Case 1

A 44-year-old male was pulled over for leaving his lane of travel and improper use of a
upon contact, the officer noticed that the subject seemed unfocused and slow. During questioning, the subject changed his answers for what he was doing several times. He was asked to submit to SFSTs and consented. However, the subject became very aggressive and was taken into custody. The subject stated that he was bipolar and was self-medicating with gabapentin and Seroquel (quetiapine). Quetiapine was not detected in the initial alkaline assay (LOD = 0.25 mg/L). The results showed < 2.0 mg/L gabapentin.

Case 2
A 24-year-old female was stopped for crossing the centerline and almost causing a collision. The officer noted the subject was very impaired with thick, slurred speech and slow reactions. The subject had a bag containing prescription bottles for gabapentin (300 mg), Celexa (20 mg), and Seroquel (100 mg). She admitted to taking gabapentin at 4:00 p.m. the day of the incident, Celexa (citalopram) at 8:00–9:00 a.m. the morning of the incident, and Seroquel (quetiapine) at 9:00 p.m. the prior night. The initial stop was at 6:30 p.m., and the DRE evaluation began at 7:13 p.m. and ended at 8:05 p.m. The officer noted that the subject appeared to be falling asleep at several points throughout the exam, and her speech was so slurred that she was almost unintelligible.

Quetiapine was not detected in the initial alkaline assay (LOD = 0.25 mg/L). The results showed 15.5 mg/L gabapentin, 0.07 mg/L citalopram, and 6 ng/mL carboxy-THC.

Case 3
A 51-year-old male was involved in a two-car collision. He was observed to have slow and deliberate movements and appeared to be lethargic. The results showed 2.5 mg/L gabapentin.

Case 4
A 24-year-old male was stopped for erratic driving and slow speeds/erratic braking. The subject’s overall demeanor was subdued and lethargic. He had scattered thoughts and difficulty answering basic questions. The subject was under the care of a psychiatrist and stated the doctor had been adjusting the doses of his prescriptions lately. The results of this case showed 4.4 mg/L gabapentin.

Discussion
The rise of gabapentin prescriptions for off-label use will lead to more frequent use of this drug in the general population. Therefore, it is important to be able to interpret if therapeutic concentrations of this drug can impair driving performance. Gabapentin is not a drug that is routinely screened for in a forensic setting. If an officer is able to recognize the signs or symptoms of this drug, they can communicate to the testing laboratory the need for additional tests necessary for gabapentin detection.

Table I. Age and Sex Distribution of Gabapentin Positive Cases in 2003–2007

<table>
<thead>
<tr>
<th>Driving Cases</th>
<th>N</th>
<th>Age (years) mean ± SD</th>
<th>Gabapentin conc. (mg/L) mean ± SD (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68</td>
<td>43.5 ± 12.0</td>
<td>7.5 ± 4.5 (5.8)</td>
</tr>
<tr>
<td>Female</td>
<td>69</td>
<td>42.4 ± 9.8</td>
<td>9.2 ± 5.8 (8.2)</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>43.0 ± 10.9</td>
<td>8.4 ± 5.4 (7.0)</td>
</tr>
</tbody>
</table>

Table II. Summary of Psychophysical Tests from Drug Recognition Expert Evaluations

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin conc. (mg/L)</td>
<td>&lt; 2.0</td>
<td>15.5</td>
<td>2.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Horizontal Gaze</td>
<td>n/a*</td>
<td>6/6</td>
<td>6/6</td>
<td>4/6</td>
</tr>
<tr>
<td>Nystagmus (HGN)</td>
<td>6/6</td>
<td>7/8</td>
<td>4/8</td>
<td>1/8</td>
</tr>
<tr>
<td>Walk and Turn (WAT)</td>
<td>4/8</td>
<td>7/8</td>
<td>4/8</td>
<td>1/8</td>
</tr>
<tr>
<td>One Leg Stand (OLS)</td>
<td>4/4</td>
<td>3/4</td>
<td>3/4</td>
<td>1/4</td>
</tr>
</tbody>
</table>

* Subject in Case 1 was unable to keep eyes open for complete HGN test.

Table III. Summary of Clinical Indicators from Drug Recognition Expert Evaluations

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin conc. (mg/L)</td>
<td>&lt; 2.0</td>
<td>15.5</td>
<td>2.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Pulse* (bpm)</td>
<td>124, 120, 98, 96, 76, 80, 84, 78, 60–90</td>
<td>118</td>
<td>94</td>
<td>76</td>
</tr>
<tr>
<td>Body temperature (°F)</td>
<td>97</td>
<td>96.6</td>
<td>97.3</td>
<td>96.98</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>150/114</td>
<td>130/84</td>
<td>168/74</td>
<td>122/76</td>
</tr>
<tr>
<td>Pupil size (mm; left/right eye)</td>
<td>Room light</td>
<td>6.5/6.5</td>
<td>5.5/5.5</td>
<td>5.5/5.5</td>
</tr>
<tr>
<td>Dark</td>
<td>7.5/7.5</td>
<td>8.0/8.0</td>
<td>9.5/9.5</td>
<td>8.0/8.0</td>
</tr>
<tr>
<td>Direct light</td>
<td>4.0/4.0</td>
<td>4.0/4.0</td>
<td>4.5/4.5</td>
<td>4.0/5.0</td>
</tr>
</tbody>
</table>

* Pulse is measured at three separate times.
The form accompanying blood evidence submitted to WSTL requests police agencies to indicate any drugs suspected or known medications of the individual. Of the 137 cases in this study, gabapentin was listed on the form for 130 (95%). This statistic may indicate that the drug is being used more often by the driving population, but without admission by the suspect or medication history, detection is missed by the toxicologist. The remaining seven cases had the presence of the gabapentin breakdown product in the initial alkaline assay, so further testing for gabapentin was performed. Overall, the breakdown product was observed in only 44 (32%) of the cases that were positive for gabapentin. This indicates that absence of the breakdown product is not a reliable predictor of whether gabapentin will be detected in a case.

The therapeutic range for gabapentin in plasma is 2–20 mg/L (14). The therapeutic range is based on studies in plasma, whereas this study examined blood samples; the plasma/blood ratio for gabapentin is unknown. This range has a wide window with dosage being intervariable between patients (16). This study observed that the mean and median concentrations of gabapentin detected in drivers were within this range for 97% of the cases. The case histories demonstrated significant driving impairment with therapeutic concentrations of gabapentin. In addition, gabapentin is rarely the only drug taken; 93% of gabapentin-positive driving cases were positive for more than one class of drugs capable of causing impairment. The most common drugs identified were methadone (15%), hydrocodone (15%), cannabinoids (15%), citalopram (15%), nordiazepam (14%), diazepam (12%), and lorazepam (12%).

A DRE evaluation is performed to determine if a subject is impaired and what category of drugs may be causing this impairment. The standard exam tests psychomotor skills by utilizing the battery of tests employed in the SFSTs: horizontal gaze nystagmus (HGN), walk and turn (WAT), and one leg stand (OLS). Performance on these tests is measured using standard clues. Research has shown that observation of four out of six clues for HGN, two out of eight clues for WAT, or two out of four clues for OLS are strong indicators of a subject having a blood alcohol level greater than 0.08 g/100 mL (18). Although these results have only been validated for alcohol, the tests are general indicators of cognitive and psychomotor ability and are still relevant for assessing impairment due to drug use.

In addition, the following vital signs are measured: pulse, blood pressure, and temperature. Pupillary diameter is measured under three conditions: room light, near darkness, and direct light. The results of these tests are compared to a matrix to determine for which drug category the indicators they observed are consistent. For example, depressants typically have HGN present, normal pupil size, lowered pulse rate and blood pressure, and normal body temperature. In addition, subjects perform poorly on the WAT and OLS. Often, the DRE assessment is able to give a toxicologist an idea of how to direct the analysis.

The DRE evaluations in this study demonstrated that gabapentin was consistent with depressants for some indicators; HGN was observed and subjects performed poorly on the WAT and OLS. However, there were some notable exceptions to the matrix. The primary difference in indicators for gabapentin was the presence of dilated pupils. Each case had at least one light condition with dilation outside the normal range, and all of the cases had values in the higher end of the range for all light conditions. In addition, a lower body temperature, and elevated pulse and blood pressure were also observed but not as consistently across the case histories. This is important for officers to be aware of when trying to assign drug classes. They may observe the indicators of a CNS depressant for the psychomotor tests but conflicting indicators for the vital signs. This scenario is similar to the DRE exception for carisoprodol for which dilated pupils are observed although the drug is a CNS depressant.

Overall, these data demonstrate that gabapentin is a commonly encountered drug that is capable of causing driving impairment even at therapeutic levels. In addition, the drug is frequently taken in conjunction with numerous other medications. Law enforcement and scientists need to be aware of the signs of gabapentin use in order to accurately direct their analysis. Also, because of the increased prescribing of this drug, doctors and pharmacists need to be aware of the impairing effects of this drug and counsel their patients accordingly.

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References